REMARKS

Claims 37 and 40-43 presently appear in this case. No claims have been allowed. Claims 37, 40 and 41 have been withdrawn from consideration. The official action of September 21, 2007, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a method for treating a disease, disorder or injury in the eye, which is other than an autoimmune disease of the eye. The disease, disorder or injury is treated by immunizing the individual having such a disease, disorder or injury with a peptide within the sequence of the pathogenic self antigen S-Ag or a modification thereof. The claims specify the preferred peptides to be administered. Preferably, the disease, disorder or injury is glaucoma.

All of the nonelected claims, other than claims 37, 40 and 41, have now been deleted without prejudice toward the filing of a divisional application. However, if present claim 43 is found to be allowable, then it is expected that claims 37, 40 and 41 will be rejoined and also found to be allowable.

Priority

The examiner acknowledged applicant's claim for the benefit of a prior-filed application parent provisional

application 60/367,271, filed on March 26, 2002, under 35 USC 119(e) or under 35 USC 120, 121 or 365(c). Applicant confirms the examiner's observation that support for the peptide of TSSEAATE (SEQ ID NO: 5) of claim 38 is found only in PCT/IL03/00251, filed March 25, 2003, and this is the effective priority date for claims that specify that embodiment.

Claim Rejection under 35 USC 112, first paragraph

Claims 30-33, 36, 38, 39 and 42 have been rejected under 35 USC 112, first paragraph, as failing to comply with the written description requirement. The examiner states that the claimed invention is directed to a method of treating a disease, disorder or injury, the method comprising the immunization of an individual with an antigen. The examiner is of the opinion that there is lack of support for the genus of immunogenic peptides that possess the claimed functional properties that are pathogenic, and pathologically and immunologically protective upon vaccination for use in the claimed method to treat an enormous genus of etiologically and pathologically distinct diseases, disorders and injuries. The examiner cites case law to argue that the specification does not clearly allow persons of ordinary skill in the art to recognize that the inventors invented what is claimed and that

the disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. The examiner states that, in analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. The examiner concludes that, in the instant case, the peptide TSSEAATE (SEQ ID NO: 5) is the only species whose complete structure is disclosed to be immunogenic. This rejection is respectfully traversed.

Respectfully, the examiner is incorrect in stating that the peptide TSSEAATE is the only species whose complete structure is disclosed to be immunogenic. All sequences disclosed in the present application, except TSSEAATE and DTALASST (SEQ ID NO:7), were disclosed previously in US Patent No. 5,961,977, cited in the present application in the paragraph bridging page 9 and 10, and which has been incorporated by reference as if fully disclosed in the present application, and were shown therein to cause proliferation of lymphocytes, i.e., the peptides are already known to be immunogenic.

The examiner further observed that, while the claims require the peptide to be a pathogenic self-antigen (claims

30(a), 32-33 and 36), the instantly elected peptide embodiment TSSEAATE (SEQ ID NO: 5) is considered by the art to be non-pathogenic (Singh et al. J. Immunology 152:4699-4705, 1994). This allegation will be discussed below, in the context of the enablement rejection.

The examiner objects that the specification and claims do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions that may be made to SEQ ID NO: 5, or any peptide. Thus, the examiner considers that the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The examiner points out that it is not clear from the specification what modifications to the peptides are necessary to obtain the required function in the claimed method, or which sequences are necessary to distinguish pathogenic from non-pathogenic properties. These points have been made moot by the present amendment to the claims.

The examiner cites the Revised Interim Guidelines in support for the written description rejection, and reminds applicant that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. Even though this may be true, our

response to the written description rejection is identical to our response to the enablement rejection and the below response to the enablement rejection will adequately address all of the above written description issues raised by the examiner.

Claim Rejection under 35 USC 112, first paragraph

Claims 30-33, 36, 38, 39 and 42 have been rejected under 35 USC 112, first paragraph, because the specification, while being enabling for a method for protecting retinal ganglion cells from secondary degeneration and death induced as a consequence of axonal injury or glutamate toxicity in Fisher rats, the method comprising the administration of an immunogenic peptide consisting of the amino acid sequence of TSSEAATE (SEQ ID NO: 5), it does not reasonably provide enablement for methods of treating an enormous genus of etiologically and pathologically distinct diseases, disorders of injuries in an enormous genus of physiologically distinct organs susceptible to T-cell mediated specific autoimmune disease, the methods comprising the administration of an enormous genus of structurally undisclosed peptide antigens so as to block the T-cell response of immunopathogenic self-antigens.

The examiner cites the *Wands* factors to systematically analyze whether the specification is enabling by looking into the breadth of the claims, the existence of working examples, the state of the prior art and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue".

First, the examiner analyses the breadth of the claims and the nature of the invention. The examiner is of the opinion that the treatment method claims are broad for encompassing an enormous genus of etiologically and pathologically distinct diseases, disorders or injuries that may occur to an organ susceptible to a T-cell-mediated specific autoimmune disease and provides a very long list of organ-specific autoimmune diseases. Furthermore, the examiner alleges that, with respect to the pathogenic self-antigen or peptide, the claims are broad for the same reason presented above in the written description rejection. The examiner also gives a brief description of the inventive concept of the invention.

Second, the examiner reviews the existence of working examples and the amount of direction provided by the inventor (page 10). The examiner states that the claims are drawn to a method of treating a disease, disorder or injury, wherein said disease, disorder or injury is other than an

autoimmune disease. The examiner alleges that Schori et al. (2001) *PNAS* 98: 3398-3403, and the specification disclose (page 23, lines 1-2) that optic nerve injury crush, used in the specification to injure the optic nerve, activates an autoimmune disease. The examiner comes to the conclusion that the specification does not disclose a working example by which a peptide treats a non-autoimmune disease, nor does the specification provide a nexus between those injury models evoking an autoimmune response within which the inventive peptides are assayed, and those diseases, disorders or injuries that do not fundamentally and mechanistically evoke an autoimmune response as required by the claims. This rejection is respectfully traversed.

The autoimmune disease allegedly evoked by optic nerve injury crush in the specification, cited by the examiner above, was not in fact evoked by the crush, but by the immunization administered on the same day (see page 23, lines 4-20). Also, the relevant sentence in Schori et al. cited by the examiner does not mean that an autoimmune disease was activated. The sentence reads:

> Recent studies in our laboratory demonstrated that the death of neurons after traumatic injury to the central nervous system (CNS) can be delayed and reduced by reinforcing a T cell immune response directed against myelin-associated self-antigens….

Thus, the T cell immune response is a beneficial response, attempting to repair the injured tissue, not a detrimental T cell immune response that activates an autoimmune disease, and the examiner's allegation is therefore not relevant.

The examiner repeats the observation, now in the context of the lack of enablement rejection, that the instantly elected peptide embodiment of SEQ ID NO: 5 is considered to be non-pathogenic (Sing et al.) and is thus not a pathogenic self antigen as required by the limitation of claim 30(a), 32, 33 and 36. The examiner also states that Figure 4 shows that the immunogenic peptide SEQ ID NO: 5 works in Fischer rats, but not Lewis rats, and draws the mistaken conclusion that "thus, a given peptide does not work for all genetic backgrounds of individuals within a given species. The specification does not provide a nexus between genetic background of Fisher rats and enormous genetic background diversity extant in humans, nor an enabling means to identify a particular genetic background within a given organism within which the claimed immunogenic peptide will predictably function as opposed to those individuals who will experience no benefit" (last paragraph of page 10).

The examiner is mistaken because Figure 4 does not show that the peptide of SEQ ID NO: 5 does not work in Lewis rats. This Figure shows that Lewis rats are sensitive to R16

immunization itself in the absence of insult; thus RGC survival was significantly lower in Lewis rats immunized with R16 than in their matched PBS injected controls. Fisher rats, on the other hand, that are resistant to the autoimmune effect of the immunization, showed no loss of RGCs in wake of R16 immunization. We would like to draw the examiner's attention to Figures 2 and 3 that show that R16 immunization of all three rat strains tested resulted in good protection from nerve crush injury.

The examiner repeats the allegation, now in the context of the lack of enablement rejection, that the specification does not disclose how to identify those pathogenic peptides that are protective upon vaccination to an enormous genus of etiologically and pathologically distinct injuries and diseases (page 11, second paragraph).

Although applicant disagrees with the examiner, in order to accelerate the procedure, applicant has amended the claims so as to limit their scope to peptides of SEQ ID NOs: 4-14, comprised within the sequence of S-Ag or derived therefrom. Direct support for the efficacy of peptides of SEQ ID NOs: 4-7 is found in Examples 1-3, and indirect support for the efficacy of peptides of SEQ ID NOs: 8-14 is based on the fact that these peptides are comprised with the sequence of S-Ag, certain sequences of which are shown in the present

application to be effective in protecting the eye, and in US 5,961, 977, which is incorporated by reference as if fully disclosed in the present application. The '977 patent shows that the peptides of SEQ ID NOs: 8-14 are immunogenic and thus they would be expected by a person with ordinary skill in the art to be effective in protecting the eye from injury, since it is proven in the present application that the protective and destructive autoimmune responses share the same antigenic specificity since a pathogenic, uveitis-related retinal self-antigen can protect against direct and indirect insults to the RGC. The examiner's rejection of the claims with respect to the pathogenic self-antigen or peptide as being too broad should now be moot.

In the analysis of the state of the prior art, the level of one of ordinary skill in the art and the level of predictability in the art, the examiner first recites the known facts lying behind the rationale for the present invention regarding the beneficial autoimmune response that can be used to protect against CNS insults by modulating - not suppressing - the immune response, citing Fisher et al., *J. Neurosci.* 21(1): 136-142; pg 141, col. 1, ¶2, and Schwartz et al., *Trends Neurosci* 28:297-302, 2003. Then the Examiner presents a list of variables that allegedly influence the inflammatory response, such as the animal species, gender and

the genetic background of the individual and cites Schwartz et al. pg 298, col 1, ¶3. The examiner further states that the therapeutic window of the vaccination-induced neuroprotection will be determined by the choice of peptides and the route of administration and that the type of immune cells, timing and tissue context affect immune activity and autoimmune activity differently. All this leads the examiner to conclude that it is difficult to estimate an appropriate dose for immunization of small peptide antigens because they may not have solid conformation and are always weaker antigens than that of the native polypeptide from which they are derived *in vivo* (Sing et al.). The examiner is thus of the opinion that the art recognizes significant unpredictability in the ability to design an immunomodulatory peptide for the treatment of injury or disease, especially as the method is applied to an individual of unknown genetic background, and optimization for each specific peptide to the specific subject must be empirically determined for the specific disease or injury, the genetic background of the subject in need and the timing and dosing of the intended peptide so as to achieve a clinically meaningful result. The examiner concludes that, in view of the breadth of the claimed immunogenic peptides, one of ordinary skill in the art would reasonably recognize significant unpredictability in identifying an amino acid

sequence *a priori* that fulfils the therapeutic function of the claimed invention.

The examiner continues in the analysis of the quantity of any necessary experimentation to make or use the invention (page 13) to claim that the guidance from the specification must provide necessary dose, timing and route of administration for an enormous genus of individuals having distinctly different genetic backgrounds and thus distinctly different immunological responses to the immunogenic peptide, so as to achieve a clinically meaningful and therapeutic result. The examiner then cites case law (e.g. *In re Gardner*) in support for the above allegations, and also repeats the opinion that the results obtained using the peptide of SEQ ID NO: 5 to protect RGC from degeneration cannot be correlated with the claimed enormous genus of structural diverse peptides for the use in treating an enormous genus of etiologically and pathologically distinct diseases, disorders and injuries in an enormous genus of genetically diverse subjects. The examiner is of the opinion that it would have required undue experimentation to make and/or use the invention to the full scope as claimed and cites *Ex parte Maizel,* 27 USPQ2d 1662, in support. The examiner then concludes "…limiting the claimed invention to a method for protecting retinal ganglion cells from secondary degeneration and death induced as a consequence

of axonal injury or glutamate toxicity in Fisher rats, the method comprising the administration of an immunogenic peptide consisting of the amino acid sequence TSSEAATE (SEQ ID NO: 5), is proper."

The Examiner's proposal to limit the claims supposedly for use in Fisher rats is unacceptable and not logical. Patent applications concerning drugs are not filed to protect treatment of rats! If the idea is that experiments in humans have to be presented, this is a requirement beyond the authority of the Patent and Trademark Office. As stated in MPEP 2107.01:

> The Federal Circuit has reiterated that therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs to be marketed in the United States.
>
> > FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. *Scott [v. Finney*], 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 [(Fed.Cir. 1994)]. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research

> and development, potential cures in many crucial areas such as the treatment of cancer.
>
> *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995).

In addition, even the FDA does not require that a drug to be marketed has first to be empirically optimized for each subject in need. Many drugs are approved for marketing even though it is known that only a fraction of the patients in need respond to said drug. The examiner has no authority to require that clinical trials must be conducted and used as evidence to provide enablement for method of treatment claims. If necessary, the Examiner's attention could be drawn to countless examples of US patents granted for drugs now marketed that are supported in the description by results obtained in animal models such as those of the present application.

In this regard, the inventors have provided ample evidence that should be considered to be fully sufficient as support for the presently amended claims; the peptides of the claimed invention were shown to be effective against direct and indirect insults to the CNS nerve cells in animal models accepted to reflect CNS damage in humans. The rats successfully treated according to the present invention were of three different strains with varying susceptibility to autoimmune disease and with various genetic background, thus

providing strong evidence for the general concept of the autoimmune response elicited with the peptides of the claimed invention.

Particularly in view of the fact that the claims have now been directed to the use of only specifically enumerated peptides and directed only to the treatment of non-autoimmune diseases, disorders or injuries to the eye, and in light of the above arguments, the rejections under both the written description requirement and the enablement requirement of 35 USC 112, first paragraph, should be withdrawn. Reconsideration and withdrawal thereof are therefore respectfully urged.

Claim Rejection under 35 USC 112, second paragraph

Claims 30-33, 36, 38, 39 and 42 have been rejected under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention. The examiner is of the opinion that the claims are vague in that no step in the claimed method refers back to or recapitulates the preamble of clam 30. The examiner states that applicant recites a method of treating a disease in an organ comprising the step of immunizing an individual, but no step is recited

that actually accomplishes the preamble. This part of the rejection is respectfully traversed.

The amendments made to claim 30 (now new claim 43) make this part of the rejection moot.

The examiner states that claim 30 recites "said disease, disorder or injury is other than an autoimmune disease". The examiner considers it to be unclear whether the limitation "other than an autoimmune disease" is required only of "said disease" or is also required of "said…disorder or injury." This part of the rejection is respectfully traversed.

It is not understood how the claim could be more clear that in no case may the disease, disorder or injury being treated be an autoimmune disease. Clearly, the "other than an autoimmune disease" requirement is required for all three terms. If the examiner has any suggestion how to avoid what he perceives to be an ambiguity, applicant will be happy to consider them. Applicant can see no ambiguity in the language of the present claims. Reconsideration and withdrawal of this part of the rejection are respectfully urged.

Claims 30(part c) and 36(part c) have been rejected since the limitation "the replacement" has no antecedent basis in the claim, and since the metes and bounds of the phrase

"modified peptides having less affinity towards the T-cell receptor than the non-modified peptides" is unclear. Also, claim 31 has been rejected since the limitation "the eye" lacks sufficient antecedent basis in claim 30. This part of the rejection is respectfully traversed.

All these rejections are now moot in view of the amendments made to the claims. Reconsideration and withdrawal thereof are therefore respectfully urged.

Claim Rejection under 35 USC 102

Claims 30-32 and 39 have been rejected under 35 USC 102(b) as being anticipated by Kipnis et al (*PNAS* 97: 7446-7451, 2000) as evidenced by Jiang et al. (*Cellular Immunol.* 217: 87-94, 2002). The examiner states that Kipnis teaches a method for treating crushed optic nerves that causes degeneration of the retinal ganglion cells in the eye, the method comprising the step of immunizing rats having the injury with Cop-1 peptide (pg 7447, col. 2, Immunization). The examiner further states that the art recognizes that myelin basic protein (MBP) is a pathogenic self-antigen associated with acute idiopathic unilateral optic neuritis as well as acute relapses of the autoimmune disorder multiple sclerosis (Warren et al. *J. Neurol. Sci.* 109:88-95, 1992). The examiner also states that the art recognizes that MBP is a

pathogenic self-antigen associated with autoimmune uveitis (Jiang et al.). The examiner then alleges that the Cop-1 peptide designed to mimic MBP fulfills the limitation of a modified peptide of a pathogenic self-antigen associated with a T-cell mediated specific autoimmune disease. This rejection is respectfully traversed.

First of all, Cop-1 is a not a pathogenic self-antigen. It is a synthetic non-pathogenic polypeptide that does not induce experimental autoimmune encephalomyelitis, but suppresses the disease (see Kipnis et al. p. 7446, 1 col. last paragraph). Secondly, Cop-1 is designed to mimic MBP, it is not obtained by a modification of MBP and it does not share a specific stretch of amino acid sequence with MBP since its sequence is random. Thus, it is not encompassed within the scope of claim 30. Nevertheless, this rejection is moot in view of the amendments made to the claims. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 30-32 and 39 have been rejected under 35 USC 102(b) as being anticipated by Fisher et al. (*PNAS* 98: 3398-3403, 2001). The examiner states that Fisher teaches a method for treating eye injury, specifically optic nerve injury that causes degeneration of the retinal ganglion cells in the eye, the method comprising the step of administering a MOG peptide,

which, according to the examiner, is a self-antigen associated with a T-cell mediated specific autoimmune disease to an individual having said injury. This rejection is respectfully traversed.

This rejection is now moot in view of the amendments made to the claims. The claims do not encompass administration of a MOG peptide. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 30-32, 39 and 42 have been rejected under 35 USC 102(b) as being anticipated by Schori et al. as evidenced by Jiang et al. The examiner states that Schori teaches a method for treating an injured optic nerve, the method comprising immunizing an individual, specifically a rat, with a peptide, Cop-1, the sequence of which is comprised within the sequence of a pathogenic self-antigen, specifically myelin basic protein (MBP). This rejection is respectfully traversed.

As has already been explained above, Cop-1 is not obtained by a modification of MBP and it does not share a specific stretch of amino acid sequence with MBP. For this reason, and since the claims have been amended in response to other rejections, this rejection is moot. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

It is submitted that all of the claims now present in the case clearly define over the references of record and fully comply with 35 USC 112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By /rlb/
Roger L. Browdy
Registration No. 25,618

RLB:jmd
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
G:\BN\B\BENA\EIS-SCHWARTZ35\pto\2008-03-21Amd.doc